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Original article

One-year clinical outcomes of ticagrelor compared with clopidogrel after percutaneous coronary intervention in patients with acute myocardial infarction: From Korean Health Insurance Review and Assessment Data

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ABSTRACT

Background: Ticagrelor has been widely accepted in clinical practice for treatment of acute myocardial infarction (AMI), however its clinical safety and efficacy have not been revealed sufficiently in Asian populations.

Methods and results: Among a total 20,270 patients (age <75 years) with AMI undergoing percutaneous coronary intervention who received dual antiplatelet therapy for at least 30 days, clinical outcomes at 1 year were assessed from the database of Health Insurance Review and Assessment Service in Korea between 2013 and 2014. Ticagrelor showed a significant effect on reduction of all-cause death [stabilized inverse probability of treatment weighted (sIPTW)-adjusted odds ratio (aOR) 0.57, 95% confidence interval (CI) 0.42–0.77, $p < 0.001$]. Stroke was also reduced by using ticagrelor (sIPTW-aOR 0.58, 95% CI 0.41–0.82, $p = 0.002$). Bleeding risk was not increased by ticagrelor use. There were nearly 30% of patients who switched from ticagrelor to different P2Y12 inhibitors. Switching P2Y12 inhibitors was associated with clinical adverse events including MI, stroke, and bleeding.

Conclusions: Among patients aged younger than 75 years, ticagrelor was associated with lower incidence of all-cause mortality. Stroke risk was also reduced in patients with a prescription for ticagrelor without an increase in bleeding risk.

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Introduction

P2Y12 receptor antagonists have been widely used for secondary prevention of atherosclerotic diseases. Ticagrelor is known to have more potent effect on platelet inhibition which has a pivotal role for reducing subsequent vascular events after acute myocardial infarction (AMI) [1,2]. However, clopidogrel has been considerably utilized for treatment of AMI in Korea [3] because of concerns about more bleeding risk among Asian patients receiving antithrombotic therapy compared with other ethnicities [4]. Previous studies based on Asian populations have been debating the pros and cons of novel P2Y12 inhibitors but the results are less than conclusive because of reported substantial risk for bleeding [5], or limitation by small population [6–8]. We previously reported that the use of novel P212 inhibitors was associated with lower risk of 30-day mortality compared with clopidogrel use [3]. In this study,

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we aimed to investigate 1-year clinical outcomes with using ticagrelor after percutaneous coronary intervention (PCI) in patients with AMI in Korea.

Materials and methods

Study population

Our study used claims data from Health Insurance Review and Assessment Service (HIRA) to assess age, sex, diagnosis, procedure, surgery, and prescribed medications. We included patients admitted to healthcare providers with diagnosis of AMI and undergoing PCI during index hospitalization and prescribed clopidogrel or ticagrelor for at least 30 days. Considering rare use of potent P2Y12 inhibitors in elderly patients, we included only patients under 75 years old as in our previous study [3]. Using diagnostic codes based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), diagnosis of AMI was defined as I21, I22, and I23 codes. ST-segment elevation myocardial infarction (STEMI) was classified by I21.0, I21.1, I21.2, I21.3 and non ST-segment elevation myocardial infarction (NSTEMI) was represented by I21.4. The rest of the AMI codes were considered as unspecified myocardial infarction (MI). Fig. 1 represents study processes regarding patient enrollment and categorization. Among 27,140 patients undergoing PCI when admitted and discharged with AMI codes as a primary or secondary diagnostic code between 2013 and 2014, a total of 20,270 patients in 171 healthcare providers were finally included and categorized according to each P2Y12 receptor antagonist which was predominantly prescribed during admission and also prescribed for at least 30 days after discharge since we intended to exclude early-onset adverse events related to procedure or underlying medical condition in need of unexpected change of medication, and patients with poor adherence to medication. Because the database was kept to be encoded and unavailable to identify each individual or healthcare provider, the study was exempted from full review and approved with a waiver of informed consent requirement by the Institutional Review Board of our institute.

Antiplatelet therapy

It has been recommended for patients with AMI to be prescribed ticagrelor with a loading dose of 180 mg followed by 90 mg twice a day in Korea. Adherence to aspirin or P2Y12 receptor antagonists was assessed by proportion of days covered, defined as total days covered by prescription claims for drugs divided by study period (days from index admission to death, or 365 days), which is capped at 1 [9,10]. Patients were dichotomously categorized by using value of 0.9 as an indicative cut-off of optimal adherence for subgroup analysis [11]. Patients were regarded as maintaining given P2Y12 receptor antagonist if it was prescribed after discharge from index admission and as switching it if two or more P2Y12 receptor antagonists were prescribed during the period. The sequence of switching antiplatelet drugs was assumed by change from prescribed regimen at discharge to different P2Y12 receptor antagonist during follow-up period. Switching from clopidogrel to potent P2Y12 inhibitors such as prasugrel or ticagrelor was considered as 'escalation'; the reverse was regarded as 'de-escalation'; and switching from ticagrelor to prasugrel was defined as 'change' among the patients who changed P2Y12 receptor antagonist after index hospitalization [12].

Study endpoints

Clinical outcomes including all-cause death, recurrent MI, stroke (including ischemic and hemorrhagic), and bleeding within 1 year after PCI were assessed. Occurrence and the date of all-cause death was identifiable from the database. Other clinical events were determined by subsequent admission with new corresponding diagnostic code after discharge from index hospitalization. Stroke was defined by a diagnosis between ICD-10-CM codes I60 to I63 and divided into hemorrhagic (I60-62) and ischemic stroke (I63). We obtained information on the bleeding events of intracranial, gastrointestinal, and other bleeding using the corresponding codes as previously described [3].

Statistical analyses

Categorical data were expressed as number (%) and analyzed with χ^2 statistics. Continuous variables were expressed as median (quartile 1, quartile 3), and were compared using the Mann–Whitney test due to skewed distribution of data. Stabilized inverse probability of treatment weighting (sIPTW) was primarily utilized to balance the differences in baseline characteristics between ticagrelor and clopidogrel groups. The other pairwise comparisons using propensity score matching (PSM) with nearest neighbor method and standardized mortality ratio weighting (SMRW) estimation [13] were adopted for further analysis. Propensity score was computed by using generalized additive logistic model with adjustment of demographic data (age and sex), comorbidities (hypertension, diabetes mellitus, heart failure, and ongoing hemodialysis), duration of index hospitalization, adherence to medications (aspirin and any P2Y12 receptor antagonists), annual number of PCI cases for AMI (PCI volume) of institution, and year at enrollment. We utilized stabilized inverse probability weights with truncation at both upper and lower 1% to reduce the risk of extremely large weights, as previously described [14]. Patients with ticagrelor and clopidogrel was matched in a 1:2 ratio for PSM analysis. We considered that comparing groups were balanced if standardized mean difference of all covariates was within 0.1 after

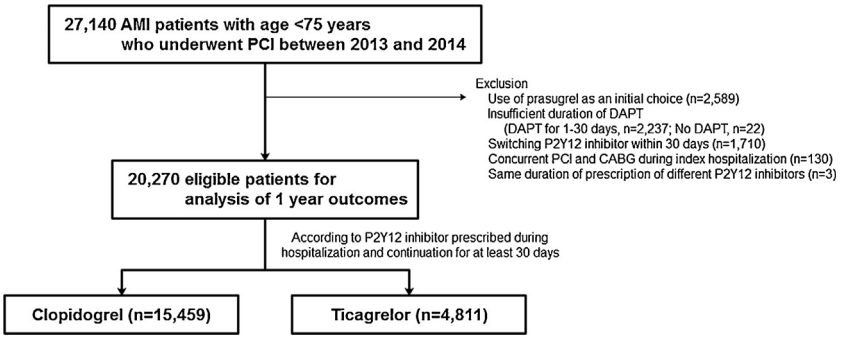

Fig. 1. Study flow, patient enrollment, assignment, and analysis. *Abbreviations*: AMI, acute myocardial infarction; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

matching or weighting. Kaplan–Meier curves and log-rank tests were used for survival comparison between the groups. The svylogrank functions from the survey package were used to calculate log-rank *p*-value in weighted cohorts [15]. Generalized additive logistic regression was used to yield the effect of each P2Y12 inhibitor on the incidence of adverse events for considering nonlinear correlation of continuous variables including age, adherence to any P2Y12 inhibitor (proportion of days covered), duration of index hospitalization, and PCI volume. In addition, age, sex, comorbidities, and year at enrollment were included as fixed effects and location (provinces) and type of healthcare provider (categorized as tertiary hospital, general hospital, hospital, and clinic) were included as random effects in the models. Subgroup analysis was also performed according to each categorical variable and dichotomously divided by median of continuous variables including age, adherence to P2Y12 inhibitors, and PCI volume. Sensitivity analysis was performed to validate different matching and weighting analyses with using different cut-off value of truncation or exclusion, and stratified analysis by each year of enrollment. All statistical analyses were performed with R Statistical Software (version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria). Values of $p < 0.05$ were considered indicative of statistically significant differences.

Results

Baseline characteristics

Baseline characteristics are summarized in Table 1. The number of patients who were categorized into clopidogrel and ticagrelor groups were 15,459 (76%) and 4811 (24%), respectively. There were some differences between clopidogrel and ticagrelor: mean age, proportions of female, diabetes mellitus, stroke, hemodialysis, and suboptimal adherence to aspirin or P2Y12 inhibitors were greater in the clopidogrel group than in the ticagrelor group. After adjustment with sIPTW, PSM, and SMRW, baseline variables were balanced except enrollment year in PSM (Supplementary Fig. 1).

One-year incidence of adverse events

The clopidogrel group (2.1%) showed higher incidence of all-cause death compared with ticagrelor group (1.1%, $p < 0.001$; Table 2). The mortality rate was significantly higher in the clopidogrel group compared with the ticagrelor group among matched and weighted cohorts [sIPTW-incidence rate difference (IRD) -0.8%, 95% confidence interval (CI) −1.2% to −0.4%, $p < 0.001$; Table 2, Supplementary Table 1] as well. Ticagrelor was associated with significantly lower incidence of all-cause death with matched and weighted models (Fig. 2, Supplementary Fig. 2). Patients with ticagrelor showed higher incidence of MI-related readmission in a sIPTW-cohort, but not in the other comparisons. Stroke-related readmission occurred in 241 patients (1.6%) in the clopidogrel group, which was higher than in the ticagrelor group (37 patients, 0.8%). After matching and weighting, the ticagrelor group had lower incidence of stroke compared with the clopidogrel group (sIPTW-IRD −0.6%, 95% CI −0.9 to −0.3%, $p < 0.001$). Crude incidence rate of bleeding-related readmission was similar, and subsequent adjusted rates also did not differ between the groups (Table 2, Supplementary Table 1).

Switching P2Y12 inhibitors and adverse events

Patients prescribed with ticagrelor (1893 patients, 39%) switched to other P2Y12 receptor antagonists more frequently than those with clopidogrel (387 patients, 3%) after discharge from index admission. Among the clopidogrel group, incidence of MI (21% vs 8%, $p < 0.001$) and stroke (3.1% vs. 1.5%, $p = 0.023$) was significantly higher in patients who were on escalated P2Y12 inhibitor regimen than those in patients who maintained clopidogrel during the entire study period (Table 3). Compared with maintaining ticagrelor, switching from ticagrelor to the other P2Y12 inhibitor within 1 year was also associated with higher incidence of adverse events including MI (11% vs. 8%, $p < 0.001$), stroke (1.2% vs. 0.5%, $p = 0.014$), and bleeding (1.4% vs. 0.6%, $p = 0.003$). A higher incidence rate of MI was found in patients

Table 1
Baseline clinical characteristics.

	Overall ($n = 20,270$)	Clopidogrel ($n = 15,459$)	Ticagrelor ($n = 4811$)	SMD	*p*-Value
Age, years	59 [51,67]	60 [52,68]	57 [50, 65]	0.213	<0.001
Male	16,633 (82)	12,499 (81)	4134 (86)	−0.137	<0.001
Hypertension	13,965 (69)	10,703 (69)	3262 (68)	0.031	0.064
Diabetes mellitus	11,310 (56)	8671 (56)	2639 (55)	0.025	0.136
Heart failure	3691 (18)	2813 (18)	878 (18)	0.001	0.950
Stroke	417 (2.1)	353 (2.3)	64 (1.3)	0.072	<0.001
Hemodialysis	305 (1.5)	279 (1.8)	26 (0.5)	0.118	<0.001
Clinical diagnosis				0.248	<0.001
NSTEMI	5147 (25)	3928 (25)	1219 (25)		
STEMI	6920 (34)	4886 (32)	2,034 (42)		
Unspecified MI	8203 (40)	6645 (43)	1558 (32)		
Antiplatelet therapy					
Aspirin					
Proportion of days covered					
Median, %	100 [96, 100]	100 [95, 100]	100 [97, 100]	0.097	<0.001
Suboptimal (<90%)	4050 (20)	3189 (21)	861 (18)	0.069	<0.001
P2Y12 receptor antagonist					
Proportion of days covered					
Median, %	100 [97, 100]	100 [96, 100]	100 [99, 100]	0.146	<0.001
Suboptimal (<90%)	3869 (19)	3113 (20)	756 (16)	0.116	<0.001
PCI volume, cases/year	125 [73, 213]	126 [72, 215]	124 [79, 196]	0.041	0.026
Duration of index hospitalization, days	7 [6, 9]	7 [6, 9]	7 [6, 9]	0.087	<0.001
Enrollment in 2013	10,115 (50)	8883 (57)	1232 (26)	0.683	<0.001

Data are presented as number (%) or median (1Q, 3Q). Standardized mean difference (SMD) was calculated as mean of each variable in clopidogrel group minus those in ticagrelor group divided by the SD of the difference.
Abbreviations: MI, myocardial infarction; NSTEMI, non-ST segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Table 2
One-year cumulative incidence rate of adverse events.

	Incidence rate (%, [events])		Incidence rate difference* (%)			
	Clopidogrel (n = 15,459)	Ticagrelor (n = 4811)	Crude	p-Value	sIPTW	p-Value
All-cause death	2.1 (319)	1.1 (51)	−1.0 (−1.4 to −0.6)	<0.001	−0.8 (−1.2 to −0.4)	<0.001
Myocardial infarction	8.1 (1245)	8.8 (423)	0.7 (−0.2 to 1.7)	0.127	1.3 (0.3–2.3)	0.012
Stroke	1.6 (241)	0.8 (37)	−0.8 (−1.1 to −0.4)	<0.001	−0.6 (−0.9 to −0.3)	<0.001
Ischemic	1.2 (187)	0.6 (27)	−0.6 (−0.9 to −0.3)	<0.001	−0.5 (−0.8 to −0.2)	0.002
Hemorrhagic	0.3 (54)	0.2 (10)	−0.1 (−0.3 to 0.1)	0.081	−0.1 (−0.3 to 0.0)	0.091
Bleeding	0.9 (136)	0.9 (44)	0.0 (−0.3 to 0.4)	0.825	0.1 (−0.2 to 0.4)	0.612

sIPTW, stabilized inverse probability of treatment weighting.
* Incidence rate difference, which was calculated by rate of ticagrelor group minus rate of clopidogrel group, was presented as % (95% confidence interval).

(16%) changing ticagrelor with prasugrel than in those having other switching patterns (de-escalation 10%, combined 11%) or maintaining ticagrelor (8%). However, there were no patients with stroke or bleeding event during follow-up in patients changing ticagrelor with prasugrel which was different with higher incidence of those events found in patients with de-escalation or combined switching (Table 3).

Risk for one-year incidence of adverse events

Adjusted odds ratios are shown in Table 4 according to different matching and weighting methods. Ticagrelor showed significant effect on reduction of all-cause death in a sIPTW-cohort (OR 0.57, 95% CI 0.42–0.77, $p < 0.001$) as well as in other cohorts. Subgroup analysis demonstrated that ticagrelor was shown to have a consistent effect toward lowering mortality across different subgroups without significant interaction between the treatment and covariates (Fig. 3, Supplementary Fig. 3). Use of ticagrelor was associated with significant reduction of all-cause (OR 0.58, 95% CI 0.41–0.82, $p = 0.002$) and ischemic stroke (OR 0.57, 95% CI 0.38–0.84, $p = 0.005$) in a sIPTW-cohort and also in the other models without increasing risk of hemorrhagic stroke. Such relevance between use of ticagrelor and lower risk of stroke was intensified in patients without switching P2Y12 inhibitors (Table 4, Supplementary Table 2). Sensitivity analysis demonstrated consistent implications of ticagrelor on clinical events even in different matching and weighting methods (Supplementary Table 3).

Discussion

We demonstrated that use of ticagrelor was associated with lower incidence of all-cause death and stroke-related readmission. Nearly 40% of patients who were initially prescribed ticagrelor did not maintain initial potent antiplatelet regimen until 1 year. Switching P2Y12 inhibitors was associated with higher incidence of adverse events including MI, stroke, and bleeding in both groups except for bleeding in patients with clopidogrel.

Lowering both cardiac and non-cardiac mortality has been demonstrated as one of the important treatment effects of ticagrelor in PLATO trial [1,16] and studies with Asian populations [6,17]. Although potential mechanisms supporting the life-saving effect of ticagrelor were suggested [16,18], some studies did not demonstrate a favorable effect of ticagrelor on all-cause mortality [2,7]. The PHILO randomized study in Asian populations reported that ticagrelor was related to at least 50% or more risk of both major or minor bleeding events, which were likely associated with higher mortality [19]. Considering the association between bleeding and other adverse events including mortality demonstrated in a previous study, utilization of ticagrelor in AMI patients who were not susceptible to bleeding may be important for obtaining a

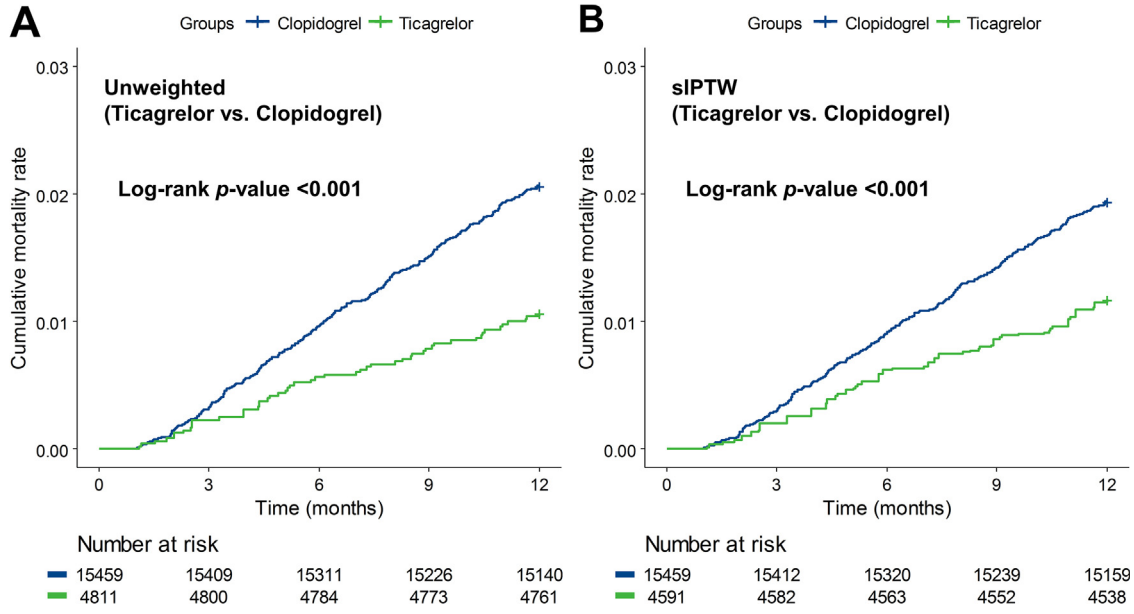

Fig. 2. Kaplan–Meier survival plot according to the use of different P2Y12 receptor antagonists. Cumulative incidences of mortality in patients ticagrelor (green) were compared with those treated with clopidogrel (blue) as a reference. Plots were demonstrated in unweighted (A) and stabilized inverse probability of treatment weighted (sIPTW, B) cohorts.

Table 3
One-year incidence of adverse events according to switching P2Y12 receptor antagonist after index discharge.

	Maintained	Switching P2Y12 receptor antagonist					*p*-Value
		All	Escalation	De-escalation	Change	Combined	
Clopidogrel							
Patients	15,072 (97.5)	387 (2.5)	387 (2.5)	–	–	–	
All-cause death	309 (2.1)	10 (2.6)	10 (2.6)	–	–	–	0.583
Myocardial infarction	1165 (7.7)	80 (21)	80 (21)	–	–	–	<0.001
Stroke	229 (1.5)	12 (3.1)	12 (3.1)	–	–	–	0.023
Ischemic	178 (1.2)	9 (2.3)	9 (2.3)	–	–	–	0.072
Hemorrhagic	51 (0.3)	3 (0.8)	3 (0.8)	–	–	–	0.316
Bleeding	130 (0.9)	6 (1.6)	6 (1.6)	–	–	–	0.248
Ticagrelor							
Patients	2918 (61)	1893 (39)	–	1344	61	488	
All-cause death	30 (1.0)	21 (1.1)	–	13 (1.0)	1 (1.6)	7 (1.4)	0.805
Myocardial infarction	219 (7.5)	204 (10.8)	–	138 (10.3)	10 (16.4)	56 (11.5)	<0.001
Stroke	14 (0.5)	23 (1.2)	–	15 (1.1)	0 (0.0)	8 (1.6)	0.014
Ischemic	7 (0.2)	20 (1.1)	–	15 (1.1)	0 (0.0)	5 (1.0)	0.002
Hemorrhagic	7 (0.2)	3 (0.2)	–	0 (0)	0 (0.0)	3 (0.6)	0.073
Bleeding	18 (0.6)	26 (1.4)	–	15 (1.1)	0 (0.0)	11 (2.3)	0.003

Data are presented as number (%).

favorable effect with ticagrelor [19]. Ours and previous studies [1,17], in favor of a reduction in all-cause mortality, demonstrated no significant increase in bleeding risk among study populations despite the concerns over bleeding risk with potent platelet inhibition by using ticagrelor. In our study, patients with ticagrelor were younger and included lower proportions of females, diabetes, and hemodialysis. We previously reported that substantial patients have likely been prescribed clopidogrel instead of potent P2Y12 inhibitors for treatment of AMI [3]. The present study also found that most patients maintained treatment with dual antiplatelet drugs for 1 year after PCI with diagnosis of AMI, but 40% of patients initially prescribed ticagrelor changed ticagrelor with another P2Y12 inhibitor, mostly with clopidogrel. These findings imply that physicians might be well aware to keep long-term dual antiplatelet therapy but to avoid significant risk of bleeding. In real-world practice in Korea, ticagrelor seems to have been properly used, in regard to selection of adequate patients or duration for maintenance of ticagrelor, to obtain clinical benefit including maximizing inhibition of thromboembolic risk in high-risk patients without marked elevation of bleeding risk. Another study of real-world patients in Korea revealed that prasugrel was associated with higher in-hospital bleeding risk without reducing ischemic events compared with clopidogrel [20]. However, more studies need to be conducted about different effects of potent P2Y12 inhibitors in Asian populations.

The importance of stroke has not been emphasized in randomized trials since 1-year incidence of ischemic stroke was reported as about 1% and treatment effect was not explored [1]. However, those studies excluded severe heart failure or rarely included patients with Killip class > II [1]. Such patients would be at higher risk for stroke [21,22] as well as overall ischemic events requiring prolonged potent antiplatelet therapy after PCI [23]. Considering 1-year incidence ranged from 2.6 [24] to 4.1% [22] reported in nationwide AMI data, stroke would occur more frequently in real-world practice, especially among high-risk patients. Given that Asians have higher risk for stroke after acute coronary syndrome than white ethnicity [21] but a lower prevalence of stroke in the general population [25], it is reasonable to assume that potential risk of stroke following AMI seems to be more augmented in Asian patients. There were some small-sized studies reporting incidence of stroke with ticagrelor use. In the result of another Korean registry, patients who were treated with ticagrelor (0.8%) suffered from stroke less frequently than those with clopidogrel (1.5%) at 6 months without statistical significance [5]. A PLATO sub-study demonstrated higher incidence of stroke in Asian (2.0%) than in non-Asian patients (1.2%) and non-significant

Table 4
Adjusted odds ratio of ticagrelor for 1-year incidence of adverse events.

Events	Unweighted		sIPTW	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
(A) Overall patients				
All-cause death	0.68 (0.50–0.93)	0.015	0.57 (0.42–0.77)	<0.001
Myocardial infarction	1.11 (0.98–1.26)	0.097	1.15 (1.02–1.29)	0.020
Stroke	0.59 (0.41–0.86)	0.005	0.58 (0.41–0.82)	0.002
Ischemic	0.55 (0.36–0.85)	0.007	0.57 (0.38–0.84)	0.005
Hemorrhagic	0.75 (0.37–1.54)	0.436	0.60 (0.29–1.23)	0.162
Bleeding	1.15 (0.80–1.65)	0.453	1.11 (0.78–1.57)	0.555
Events	Unweighted		sIPTW	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
(B) Patients without switching P2Y12 receptor antagonist during follow-up period				
All-cause death	0.71 (0.48–1.05)	0.083	0.59 (0.41–0.87)	0.007
Myocardial infarction	0.95 (0.81–1.11)	0.528	0.98 (0.84–1.14)	0.785
Stroke	0.40 (0.23–0.70)	0.001	0.40 (0.23–0.67)	0.001
Ischemic	0.26 (0.12–0.57)	0.001	0.29 (0.15–0.58)	<0.001
Hemorrhagic	0.91 (0.40–2.08)	0.823	0.67 (0.28–1.61)	0.373
Bleeding	0.77 (0.46–1.28)	0.308	0.61 (0.35–1.06)	0.077

Abbreviations: CI, confidence interval; sIPTW, stabilized inverse probability of treatment weighted; OR, odds ratio.

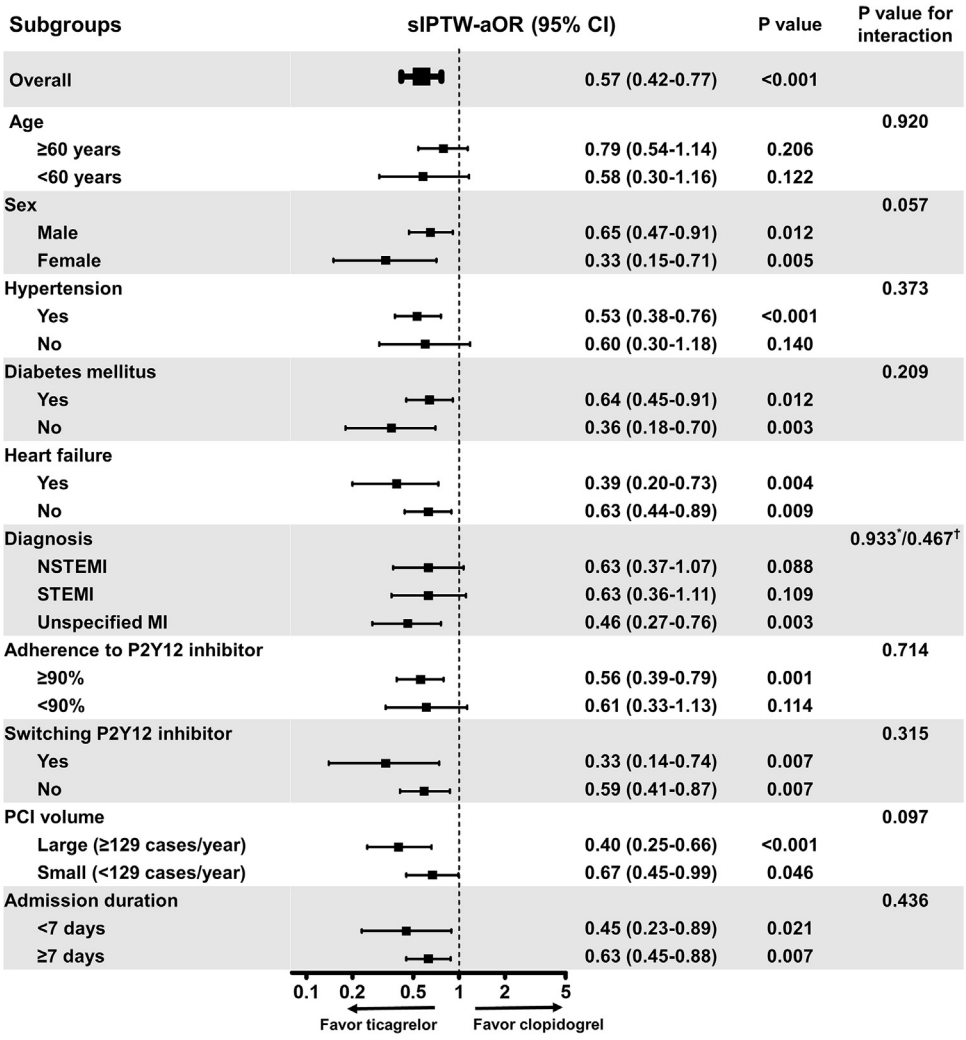

Fig. 3. Subgroup analysis of the effect of ticagrelor on all-cause death. Adjusted odds ratio (aOR) presented according to covariates using stabilized inverse probability of treatment weighting (sIPTW). *p*-Values indicate interactions between NSTEMI vs. STEMI (*); and NSTEMI vs. unspecified MI (†). *Abbreviations*: CI, confidence interval; MI, myocardial infarction; NSTEMI, non-ST segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

reduction of stroke by ticagrelor among East Asian patients (1.5% vs. 0.7% = clopidogrel vs. ticagrelor) [6]. The role of potent P2Y12 inhibitors for the purpose of secondary prevention of stroke has not been established. Especially, prasugrel is contraindicated in patients with history of stroke or transient ischemic attack due to substantial bleeding risk without a preventive effect on ischemic events. In contrast to prasugrel, ticagrelor was revealed to have a constant benefit for secondary prevention in patients with AMI irrespective of prior ischemic stroke [26]. It has also been suggested to have a benefit to reduce the risk of stroke in patients with prior MI [2]. Among patients with acute cerebral ischemia, ticagrelor was not superior to aspirin in reducing composite endpoints including stroke, MI, or death at 90 days, whereas subgroup analysis revealed a significant effect of ticagrelor on reduction of composite endpoints in Asian patients [27]. Further investigation regarding the role of ticagrelor in secondary prevention of ischemic stroke should be followed in Asian patients.

Switching P2Y12 receptor antagonist was more frequent among patients with ticagrelor in our study. Prospective registries reported that escalation of antiplatelet therapy after discharge was uncommon and mostly owing to adverse events related to prior drug, hemorrhage, economic burden, and physician's recommendation [28,29]. Escalation of antiplatelet therapy commonly occurred in the catheterization laboratory at the time or immediately after PCI, which might be related to high-risk angiographic characteristics or ischemic adverse events [12]. Otherwise, de-escalation might have contributed to high bleeding risk or events, drug-related adverse effects, or economic burden. Since the reasons and associated adverse events were not assessed in our study, further investigations will be able to provide clinical implications regarding switch of P2Y12 receptor antagonists. In addition, considering the high risk of ischemic and hemorrhagic events in both early and late periods after AMI [30], modified strategies for dual antiplatelet therapy such as 'guided de-escalation' would be worthy in clinical practice [31].

There are some limitations to our study. First, we could not assess laboratory, angiographic, or procedural data. Higher risk for recurrent MI including coronary lesion and procedural characteristics might demand more potent antiplatelet therapy, whereas clopidogrel would be preferred among patients with high risk for bleeding. The bias might lead to higher risk for recurrent ischemic events and lower risk of bleeding events among patients with a portent P2Y12 inhibitor. It might not be insufficient to adjust such unrevealed confounders and that might result in null effect of ticagrelor on recurrent MI or bleeding in the present study. We tried to adjust differences in baseline characteristics determined in

our database with matching and weighting methods, although potential bias could not be negligible and it would require a cautious interpretation of the results. Second, time-dependent analyses were available only for mortality, and we could analyze occurrence of the other adverse events at re-admission with corresponding diagnosis. In addition, because only patients who continued dual antiplatelet therapy for at least 30 days were eligible, any mortality within 30 days was not included in the study. Early events during index admission which could be associated with critical medical condition or procedures were not considered. Therefore, it should be considered that most clinical events assessed in the study might not have occurred earlier than acute phase of AMI. Also, incidence of such events may be steadily increasing along a similar line as demonstrated in previous studies [32,33]. Third, this study did not include information about atrial fibrillation and the use of oral anticoagulants, which might be associated with higher risk of stroke and the choice of switching of P2Y12 receptor antagonist toward the use of clopidogrel. It might also weaken the true effect of ticagrelor on the other adverse events. Finally, we determined clinical outcomes by diagnostic codes for readmission except mortality. Diagnoses regarding adverse events were not based on predefined criteria but left to the decision of each clinician, and it was also limited to evaluate severity of stroke. It is necessary to assess this in future studies for supporting our results.

Conclusions

Among real-world patients with AMI who underwent PCI and continued initial dual antiplatelet regimen for at least 30 days afterwards, ticagrelor was associated with lower incidence of all-cause death until 1 year compared with clopidogrel in Korea. Use of ticagrelor was related to a reduction in incidence of stroke-related readmission without a significant increase in bleeding risk. The findings need to be attentively interpreted that elderly patients (aged 75 years or more) who may be at higher risk of bleeding with potent antiplatelet therapy were not included in the study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.08.005.

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